

Claim Rejections 35 USC 112, second paragraph

Responsive to the Examiner's objections, the claims have been amended. In the following remarks, applicant serially addresses the rejections and comments on the amendments.

First, claim 1 has been rejected because it appears that the "activatable layer is locally in contact to a portion of the specimen." This claim as amended now requires that the selectively activatable layer overlies the specimen "without contacting the specimen." Thus it is clear that before activation no part of the selectively activatable layer is in contact with the specimen.

Secondly, the claim has been objected to as not containing the requisite "microdissection." Simply stated, the preamble refers to "microdissection." The body of the claim did not contain steps setting forth microdissection. A "separating" step has been added at the bottom of the claim which clearly carries out the referred to microdissection.

Claim 3, line 3 has been objected to at the phrase "visualizing the specimen" because it is unclear what antecedent portion of the specimen is being visualized. Language has now been added to clarify the visualizing step. This language is "visualizing the portion of the specimen to locate the portion of the specimen for microdissection.."

In claim 3, the claim has been criticized for failing to distinctly define how this step of selective activation in the claim 3 is distinct from the selective activation performed in claim 1. An explanation has been requested.

In claim 1, the step of visualizing is omitted. A small portion of the specimen is microdissected. In claim 3, visualization is used to locate the portion of the specimen to be microdissected.

In claim 5, the term "surface" has been replaced with -- coating --. Further, the "coating" is now claimed as being on the selectively activatable layer and exposed towards the specimen. The specification makes clear that so-called "affinity specific" coatings are well known. By the expedient of contacting the specimen with such affinity specific coatings, selective adherence of portions of the specimen to the activatable layer can occur.

Claim 6 has been criticized for failing to properly defined the repeated steps. The criticism of the Examiner is well taken. The claim has now been amended to include the specific recitation of the "placing, selectively activating, and separating steps."

Claim 6 has been further criticized as to the language "different target elements within the specimen." The claim now makes clear that the repeated steps occur with "different parts of the selectively activatable layer to capture a series of portions of the specimen on the selectively activatable layer."

Claims 7 has been rejected because of the "moving" step. The claim now makes clear that the moving of the selectively activatable layer followed by microdissection can concentrate the series of portions on the activatable layer. Thus, although the portions were spaced in the original specimen, they can be concentrated once collected to the selectively activatable layer. Concentration is thus achieved.

Claim 8 has been criticized as missing a correlation step that refers back to the requirements of the preamble. The preamble has now been modified to read "A process of attachment of a selectively activatable layer to a portion of a specimen having the steps of:" It can be understood that the process of attachment of the selectively activatable layer has specific utility. For example, later separation of the selectively activatable layer from the specimen can cause extraction of the portion(s) which are adhered to the selectively activatable layer.

Claim 9 sets forth the complete microdissection step. The original adherence to the selectively activatable layer and the contraction upon cooling while maintaining adherence causes microdissection in this particular claim. In claim 8 the contraction merely caused tension to increase in the adhered portion of the selectively activatable layer. This claim covers the case where the produced tension is sufficient to cause microdissection.

Claim 10 also sets forth a complete microdissection step. Remembering that in claim 8 adherence of the selectively activatable layer occurred, claim 10 points out that tensioning of the portion of the selectively activatable layer which is adhered to the portion of the specimen can also occur. When the activatable layer is withdrawn from the specimen, the adhered portions of the specimen are microdissected.

Claim 11 is directed to raising the microdissection portions of the specimen above the remainder of the specimen through the contracting step. It can be understood that once this raising occurs, adhered portions of the specimen on the selectively activatable layer will not contact the non microdissected specimen portions. Interference between the dissected portions and the remainder of the specimen will not occur.

Claim 12 has had the objected to language removed.

Claim 14 has been redrafted. Two kinds of expansion of the selectively activatable layer are there referred to. The first expansion is the normal expansion where an extremity of the material moves away from the selectively activatable layer. A second type of expansion is referred to. In this expansion, material about the first expansion moves radially inwardly to and towards the first expansion material. This causes the first expansion material to extrude not unlike toothpaste from a toothpaste tube.

Claim 15 has been objected to because of the lack of antecedent for the "first volume." With the amendment of claim 14 it is believed that this portion of the claim is made clear.

Applicant has extensively amended claims in order to meet the objections of the Examiner. Applicant does not wish to take issue with the Examiner over claim wording. Accordingly, applicant will liberally entertain suggestions of the Examiner to further clarify the terminology utilized herein.

Rejections on the Merits

First, the Examiner maintains his rejection over Goldstein et al. U.S. Patent 6,100,051. Reconsideration is respectfully requested in view of the claims as amended.

Claims 1, 8, and 14 have all been amended to modify the "placing" step. Specifically, the language used is:

placing the selectively activatable layer overlying
the specimen at a separation less than a first interval without
contacting the specimen; (Emphasis added)

This patent application is directed among other things to so-called "noncontact laser capture microdissection." The main problem that this application seeks to solve is known as "non specific transfer." It is believed that a quick review of the dangers of non specific transfer will suffice. See the paragraph on page 14, beginning in line 15.

When contact occurs between a layer and a sample, with out the activation referred to herein, there is danger that the portions of the sample will nevertheless adhere to the activatable layer. Thus, although the researcher desires to collect one portion of

the sample, other parts of the specimen adjacent to the portion collected may be gathered with the collected portion. These other parts of the specimen are non specifically transferred and will be drawn away from the specimen with the portion that is been collected by laser capture microdissection. When this occurs, more than the desired portion of the sample is microdissected. Remembering, that where extraordinarily small portions of the specimen are going to be analyzed, such portions are frequently subjected to biological amplification (PCR). Where over inclusion of the portions occurs, the resultant amplified portion of the sample is degraded in amplification just as it was in original sample selection.

Goldstein et al. relates to contact microdissection. The surface containing the convex geometry is first contacted to the specimen and thereafter activated for the microdissection of the targeted portion of the specimen. This technique contains the ever present possibility of non specific transfer as described immediately above the.

The instant claims make clear that the selectively activatable layer is not placed in contact with the specimen, except as a result of and during the activation. By keeping the activation precise, selection of the sample portion is equally precise. Incidents of non specific transfer can be at least reduced and sometimes avoided.

New Grounds of Rejection

Rejection -- (Judicially Created) Obviousness Type Double Patenting

The Examiner has objected to the pending claims under the judicially created doctrine of obviousness-type double patenting. Claims 1 to 15 have been rejected as unpatentable over Bonner et al. United States Patent 6,420,132. The rejections states:

Claims 1-15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 8-11, and 15-20 of U.S. Patent No. 6,420,132. Although the conflicting claims are not identical, they

are not patentably distinct from each other because both inventions use laser radiation to activate and activatable layer by heating the layer to cause an expansion of a layer to affect contact and capture of a targeted portion of the specimen. In the case of Bonner et al. (US 6,420,132), the activatable layer expands by melting of the layer to affect contact and capture which in effect causes the vapor bubble formation, just as recited in the instant claimed inventions.

Applicant agrees with this rejection. Specifically, the filing of the Provisional Application No. 60/094, 871 entitled Precision Laser Capture Microdissection Utilizing Short Pulse Length on July 30th, 1998 constituted a constructive reduction to practice of this invention. Applicant's attorney files herewith a terminal disclaimer. It is believed to obviate the judicially created obviousness-type double patenting. Withdrawal of this rejection in light of the terminal disclaimer is respectfully requested.

Rejections -- Baer et al. U.S. Patent 5,985,085 under 35 USC 102(e)

First, Baer et al. U.S. Patent 5,985,085 is a reference cited in Bonner et al. U.S. Patent 6,420,132. As set forth in the above double patenting rejection, the invention of Bonner et al. '132 is not "patentably distinct" from the invention herein. In other words, Bonner et al. '132 constitutes a constructive reduction to practice of the invention herein.

Secondly, Declarants Robert Bonner and Dale Berkley submit in this application declarations identical to declarations lodged in the Bonner et al. '132 prosecution to overcome the Baer et al.'085 in that prosecution. Simply stated, these declarations showed due diligence between December, 1997 and the beginning of July, 1998 between applicants conception of the invention and the constructive reduction to practice on the July 30th, 1990 filing date of Bonner et al. '132 Patent.

1998

Third, and as set forth in MPEP Section 715.07 (a), this is all the due diligence that need be shown. Specifically, only diligence before the reduction to practice is a material consideration. The "lapse of time between the completion or reduction to practice of an invention and the filing of an application there on" is not relevant to an affidavit or declaration under 37 CFR 1.131. See *Ex Parte Merz*, 75 USPQ 296 (Board of Appeals, 1947). Accordingly, it is respectfully requested that the *Baer et al.* '085 reference be withdrawn.

The Declarations Briefly Summarized

First, applicant incorporates the Declarations of Dr. Robert Bonner and Dr. Dale Berkley into these remarks as if fully set forth herein. This is done to avoid rejection on the grounds of disparity between a summary of the Declarations and the Declarations themselves.

Second, reduction to practice requires showing that the apparatus actually existed and worked for its intended purpose. In *re Asahi/America Inc.* 33 USPQ 2nd 1921, (U.S. Court of Appeals, Federal Circuit: 1995). As that decision points out, some devices are so simple that mere construction of them is all that is necessary to constitute reduction to practice.

The purpose of filing a 131 declaration is to demonstrate that applicant's date of invention is prior to the effective date of the reference cited in support of a rejection. (Citation) Where the reference cited in support of a rejection "substantially shows or describes *the does not claim*" the subject matter of the invention in question, (Rule) 131 allows the patent owner to overcome the reference by showing that the invention in question was reduced to practice prior to the filing date of the reference. (33 USPQ 2nd 1923)

... However, this court has held that "there are some devices so simple that a mere construction of them is all that is necessary to constitute reduction to

practice." *Sachs v. Wadsworth*, 48 F. 2nd 928,929, 9 USPQ 252, 253 (CCPA 1931). *See also King Instrument Corp. v. Otari Corp.*, 767 Fed 2nd 853, 861, 226 USPQ 402, 407 (Fed Circuit 1985) *cert. denied* 475 U.S. 1016.

Applicants submit that Dr. Robert Bonner's Declaration is exactly such a case. Given the context of laser capture microdissection, the words of paragraph number 5 are inescapable. "Presently we have had noncontact transfer - where the 100um thick film and tissues section are separated by up to 17um (and the film is below the tissue), the melted film still makes contact with the tissues/wets it/and then solidifies to form a strong focal bond with it (and the film forms a surface pedestal with the tissue on)." As the Examiner will observe, this language is precisely descriptive of embodiments set forth in the application. Furthermore, the language evidences that the contact actually worked. Applicant had possession of the invention.

Simply summarized, Dr. Bonner in his Declaration includes a full summary of the e-mail communications relating to laser capture microdissection between himself, Thomas Baer, and the subsequently formed corporation, Arcturus. This summary is offered so that the Examiner can see the context in which the disclosure of noncontact laser capture microdissection on January 7, 1997 occurred. Thereafter, the declaration explains the conduct of Dr. Robert Bonner as a thorough scientist to and until his signing of the invention disclosure on December 23, 1997.

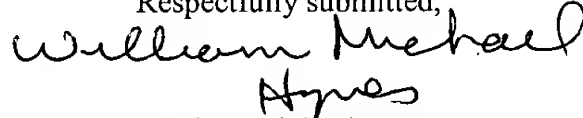
The Declaration of Dr. Dale Berkley sets forth the timely processing of the disclosure within NIH between December 23, 1997, and July 1998 when filing of Precision Laser Capture Microdissection Utilizing Short Pulse Length, Provisional Patent Application 60/094,871 was authorized. As the application was filed as a Provisional Patent Application on July 30, 1998 and ultimately became US Patent 6,420,132, no further evidence of timeliness is tendered.

It is submitted that the Declarations "swear behind" Baer et al.' 085. All pending claims are submitted to be allowable.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at .

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (~~One~~Twice Amended) A process of laser capture microdissection of at least a portion from a specimen having the steps of:

providing a selectively activatable layer which upon activation causes volumetric expansion with an extremity of the volumetric expansion exceeding a first interval taken normal to a surface of the selectively activatable layer, the extremity becoming adhesive to a portion of the specimen upon selective activation;

placing the selectively activatable layer overlying the specimen at a finite separation less than the first interval without contacting the specimen;[-and,]

selectively activating the selectively activatable layer to cause volumetric expansion at least to the first interval to locally contact a portion of the specimen at the extremity of the volumetric expansion[-] and become adhesive to the portion of the specimen; and,

separating the selectively activatable layer from the specimen to micro dissect the portion of the specimen from the remainder of the specimen.

what happened to the specimen?

3. (~~One~~Twice Amended) The process of laser capture microdissection from a specimen according to claim 1 having the steps of:

visualizing the portion of the specimen to locate the portion of the specimen for microdissection; and,

activating the selectively activatable layer overlying the visualized portion of the specimen.

5. (~~One~~Twice Amended) The process of laser capture microdissection from a specimen according to claim 1 having the steps of:

placing a [~~surface~~]coating on one side of the selectively activatable layer [~~exposed to the specimen~~] having an affinity specific bond with at least one part of the specimen;

exposing the selectively activatable layer at the coating to the specimen;
and,

activating the selectively activatable layer to cause the [surface]coating
having the affinity specific bond to contact the specimen and form affinity specific
[bonds]bond with the [portion]at least one part of the specimen~~[-having the specific~~
~~surface affinity defined by the surface]~~ on the activatable layer.

6. ([One]Twice Amended) The process of laser capture
microdissection from a specimen according to claim 1 having the steps of:
repeating the placing, selectively activating [of],and separating steps at
different portions of the specimen with different parts of the selectively activatable layer
to ~~[cause corresponding contact and-]~~capture a series of ~~[different targeted elements~~
~~within]portions of~~ the specimen on the selectively activatable layer.

7. ([One]Twice Amended) The process of laser capture
microdissection from a specimen according to claim 6 having the steps of:
moving the selectively activatable layer with respect to the specimen to
micro dissect and concentrate the series of [captured elements]portions on the activatable
layer ~~[compared]~~relative to ~~[their]~~the series of portions spacing within the specimen.

8. ([One]Twice Amended) A process of ~~[laser capture~~
~~microdissection]~~attachment of a selectively activatable layer to a portion ~~[from]~~of a
specimen having the steps of:

providing a ~~[laser activated-]~~selectively activatable layer having which
upon laser activation causes heat generated volumetric expansion of an extremity to a
first interval taken normal to the surface of the selectively activatable layer and upon
cooling elastically contracts~~[-an]~~ the extremity towards the activatable layer; the
extremity of the volumetric expansion ~~[exceeding a first interval taken normal]~~having
adhesive properties with respect to a [surface of the selectively activatable layer]portion
of the specimen during and after activation;

placing the selectively activatable layer overlying the specimen at a portion for micro dissection at a separation less than the first interval without contacting the specimen; and,

selectively activating with laser energy to heat the selectively activatable layer to cause heat generated volumetric expansion [at]of [~~least~~]the extremity to [~~the~~]a first interval taken normal to [~~locally~~]the surface of the selectively activatable layer to contact the portion of the specimen and [~~bond~~]adhere to [a]the portion of the specimen[~~at the extremity of the volumetric expansion~~];

ceasing the laser activation; and,

allowing the [~~volumetric expansion to cool~~]heated the selectively activatable layer to cool and elastically contract the extremity towards the activatable layer while maintaining adherence to the portion of the specimen.

9. ([~~Once~~]Twice Amended) The process of [~~laser capture microdissection from~~]attachment of a selectively activatable layer to a portion of a specimen according to claim 8 having the steps of:

[~~contracting the volumetric expansion to separate~~]allowing the heated selectively activatable layer to cool and elastically contract the [~~targeted~~]extremity towards the activatable layer while maintaining adherence to the portion of the specimen [~~from the specimen and~~]to thereby [~~microdissecting~~]micro dissect the portion of the specimen from a remainder of the specimen.

10. ([~~Once~~]Twice Amended) The process of [~~laser capture microdissection from~~]attachment of a selectively activatable layer to a portion of a specimen according to claim 8 having the steps of:

contracting the volumetric expansion by cooling while maintaining attachment to the portion of the specimen to elastically [~~tensioning~~]tension the volumetric expansion of the activatable layer; and,

withdrawing the activatable layer from the specimen to separate and thus micro dissect the portion of the specimen from the remainder~~[of the specimen thereby microdissecting the portion]~~ of the specimen.

11. (~~Once~~Twice Amended) The process of ~~[laser capture microdissection from]~~attachment of a selectively activatable layer to a portion of a specimen according to claim ~~[10]~~8 ~~[where]~~having the ~~[withdrawing the activatable layer step comprises]~~steps of:

contracting the volumetric expansion at the extremity to withdraw the portion of the specimen bonded to the volumetric expansion within the first interval whereby the portion of the specimen bonded to the extremity of the volumetric expansion cannot contact underlying and remaining portions of the specimen~~[when the activatable layer is maintained separate from the specimen by the first interval]~~.

12. (~~Once~~Twice Amended) The process of ~~[laser capture microdissection from]~~attachment of a selectively activatable layer to a portion of a specimen according to claim 8 having the steps of:

providing activatable layer with ~~[strong long chain thermoplastic polymers with]~~a~~[large]~~ volume change associated with phase transition.

13. (Once Amended) The process of ~~[laser capture microdissection from]~~attachment of a selectively activatable layer to a portion of a specimen according to claim 8 having the steps of:

attaching the activatable layer to a supporting substrate.

14. (Once Amended) A process of laser capture microdissection from a specimen having the steps of:

providing a selectively activatable layer which upon activation by laser causes volumetric expansion upon heating and adhesion to a specimen;

placing the selectively activatable layer overlying the specimen at a separation less than a first interval without contacting the specimen;

heating and expanding the selectively activatable layer to cause volumetric expansion first by locally heating and expanding a first inner volume of the selectively activatable layer with a component of expansion normal to the selectively activatable layer to cause an extremity of expansion away from the activatable layer; [and,]

heating and expanding a surrounding second volume of the selectively activatable layer with a component of expansion in a plane of the selectively activatable layer into the first volume whereby a total volumetric expansion occurs with the second volume expanding into and extruding the first volume at the extremity for a total expansion at least to the first interval to locally contact a portion of the specimen [at]with the extremity of the volumetric expansion[.] and adhere to the portion of the specimen; and,

removing the extremity of the volumetric expansion with the portion of the specimen attached to micro dissect the portion from the sample.

15. (~~One~~Twice Amended) The process of laser capture microdissection from a specimen according to claim 14 having the steps of:

generating ~~the~~a vapor bubble in the first volume during heating and expanding of the first volume~~[.]~~ whereby the vapor bubble contributes to the volumetric expansion of the first volume